

# The hydration free energy of water

Gerhard Hummer,<sup>\*ab</sup> Lawrence R. Pratt,<sup>c</sup> and Angel E. García<sup>a</sup>  
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We study the chemical potential of water as a function of charge based on perturbation theory. By calculating the electrostatic-energy fluctuations of two states (fully charged and uncharged) we are able to determine accurate values for the dependence of the chemical potential on charge. We find identical results for the chemical-potential difference of fully charged and uncharged water from overlapping-histogram and acceptance-ratio methods and by smoothly connecting the curves of direct exponential averages. Our results agree with those of Rick and Berne (*J. Am. Chem. Soc.*, **1994**, *116*, 3949) with respect to both the chemical-potential difference and its dependence on the charge coupling parameter. We observe significant deviations from simple Gaussian-fluctuation statistics. The dependence on the coupling parameter is not quadratic, as would be inferred from linear continuum models of electrostatics.

## I. INTRODUCTION

The accurate calculation of *thermal* properties of fluid systems such as the free energy or the entropy using computer simulations poses serious difficulties. Unlike mechanical quantities (e.g., energy, pressure) which can be expressed as averages of functions of the phase-space coordinates, *thermal* quantities are related to the partition function and thus to the volume of accessible phase space.<sup>1</sup>

We recently pursued an approach based on perturbation theory for the chemical potential which relates the free-energy difference of two states to fluctuations of the two equilibrium systems.<sup>2,3</sup> This has the advantage that along with free-energy data other useful information can be extracted from equilibrium computer simulations. Motivated by the Born-model prediction of quadratic dependence of the free energy on ionic charge,<sup>4</sup> we studied the free energy of simple ions in water. Within the framework of perturbation theory, the Born model suggests validity of a second-order treatment with the ionic charge as a coupling parameter and, correspondingly, Gaussian statistics of the electrostatic potential.<sup>5,6</sup> Our work indeed supported this view; but it also showed that to get *accurate* values for the free energy of ionic solvation it is important to combine fluctuation information of different charge states.

In this work we study the chemical potential of water. This quantity plays a central role in many processes of physical chemistry and biophysics. For instance, the chemical potential of water is the driving force in osmotic equilibria. To study inhomogeneous aqueous systems or mixtures such as macromolecular solutions or crystals using grand-canonical-ensemble methods, accurate values for the chemical potential of the particular water model are required.

We will be concerned with the electrostatic contributions to the chemical potential. Efficient methods such as test-particle insertion<sup>7</sup> are available for the contributions related to the particle volume. We will study the process of uncharging a water molecule with the van der Waals interactions unmodified. Fluctuation statistics and, for reference, Bennett's overlapping-histogram and acceptance-ratio methods<sup>8</sup> will be used to calculate the chemical potential. We also use a geometrical method which smoothly connects the direct exponential averages. We compare our results for the chemical potential with those of Rick and Berne<sup>9</sup> obtained from thermodynamic integration.

We will first develop the theoretical framework. The correction for finite system size will be discussed. As in our previous studies,<sup>3,10</sup> we will use Ewald lattice summation and a generalized reaction-field (GRF) method for the electrostatic interactions and consistently add the self-interactions as finite-size corrections. We will then describe the computer simulations and discuss the results.

<sup>a</sup> Address for Correspondence: Theoretical Biology and Biophysics Group T-10, MS K710, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, U.S.A. [FAX: (505) 665-3493; Phone: (505) 665-1923; E-mail: [hummer@t10.lanl.gov](mailto:hummer@t10.lanl.gov)]

<sup>b</sup> Center for Nonlinear Studies, Los Alamos National Laboratory, MS B258, Los Alamos, New Mexico 87545, U.S.A.

<sup>c</sup> Theoretical Chemistry and Molecular Physics Group T-12, MS B268, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, U.S.A.

## II. CALCULATION OF CHEMICAL POTENTIALS

### A. Fluctuation statistics

Various methods are available to calculate free-energy differences between different states of fluid systems using computer simulations (see refs 1,11,12 for reviews). Here we are concerned with determining the electrostatic contributions to the free energy of water. The chemical-potential difference  $\Delta\mu^{ex}$  between a charged and an uncharged water molecule in bulk water is calculated. Our goal is to relate  $\Delta\mu^{ex}$  to fluctuations in the electrostatic energy of single water molecules.

The potential-distribution theorem for the excess chemical potential  $\mu^{ex}$  forms a convenient starting point:<sup>7</sup>

$$\mu^{ex}(\lambda_1) - \mu^{ex}(\lambda_0) = -k_B T \ln \langle \exp \{ -\beta [u(\lambda_1) - u(\lambda_0)] \} \rangle_{\lambda_0} . \quad (1)$$

$\lambda_0$  and  $\lambda_1$  are coupling parameters representing the two charge states.  $\beta$  is the inverse temperature  $1/k_B T$ . The thermal configuration-space average in the charge-state  $\lambda$  is denoted by  $\langle \dots \rangle_\lambda$ .  $u(\lambda)$  is the charge- and configuration-dependent interaction energy of a water molecule carrying charges  $(1-\lambda)q_O$  and  $(1-\lambda)q_H$  on oxygen and hydrogen atoms, respectively.  $\lambda = 0$  and 1 correspond to the fully charged and uncharged state, respectively. We will only discuss results for three-point models of water. Extensions to water models carrying four and more partial charges are trivial.

The energy  $u(\lambda)$  contains the electrostatic interactions  $u_{el}(\lambda)$  with all other water molecules and a self-interaction  $u_s(\lambda)$ ,

$$u(\lambda) = u_{el}(\lambda) + u_s(\lambda) , \quad (2)$$

where

$$u_{el}(\lambda) = (1-\lambda) [q_O \phi_O + q_H (\phi_{H_1} + \phi_{H_2})] . \quad (3)$$

$\phi_O$ ,  $\phi_{H_1}$ , and  $\phi_{H_2}$  are the electrostatic potentials at the sites of the oxygen and hydrogen atoms. The self-interaction  $u_s(\lambda)$  depends on the effective electrostatic interaction  $\varphi(\mathbf{r})$  used in the computer simulations,

$$u_s(\lambda) = \frac{1}{2} \sum_{\alpha, \beta} (1-\lambda)^2 q_\alpha q_\beta \Psi(r_{\alpha\beta}) , \quad (4)$$

where the double sum extends over pairs of charge sites on a water molecule.  $\Psi$  is averaged over the solid angle  $\Omega$ ,

$$\Psi(r_{\alpha\beta}) = \int_{\Omega} d\Omega \left[ \varphi(\mathbf{r}_{\alpha\beta}) - \frac{1}{|\mathbf{r}|} \right] . \quad (5)$$

The perturbation expression eq 1 can be used directly if the  $\lambda_1$  and  $\lambda_0$  states are close. Otherwise, the average in eq 1 is dominated by the poorly sampled tails of the distribution of  $\Delta u = u(\lambda_1) - u(\lambda_0)$ . As in our previous work,<sup>2,3</sup> we use a perturbative expansion. Application of the cumulant expansion<sup>13</sup> with respect to  $\Delta\lambda = \lambda_1 - \lambda_0$  yields a series expansion for the difference in chemical potential  $\Delta\mu^{ex} = \mu^{ex}(\lambda_1) - \mu^{ex}(\lambda_0)$ :

$$-\beta \Delta\mu^{ex} = -\beta u_s(0) [\Delta\lambda (\Delta\lambda + 2\lambda_0 - 2)] + \sum_{n=1}^{\infty} \frac{(\beta \Delta\lambda)^n}{n!} C_{n, \lambda_0} [u_{el}(0)] . \quad (6)$$

The cumulants  $C_{n, \lambda_0} [u_{el}(0)]$  measure the fluctuations of the electrostatic energy  $u_{el}(0)$  in the state  $\lambda_0$ :

$$C_{1, \lambda_0} [u_{el}(0)] = \langle u_{el}(0) \rangle_{\lambda_0} , \quad (7a)$$

$$C_{2, \lambda_0} [u_{el}(0)] = \langle \Delta u_{el}^2 \rangle_{\lambda_0} , \quad (7b)$$

$$C_{3, \lambda_0} [u_{el}(0)] = \langle \Delta u_{el}^3 \rangle_{\lambda_0} , \quad (7c)$$

$$C_{4, \lambda_0} [u_{el}(0)] = \langle \Delta u_{el}^4 \rangle_{\lambda_0} - 3 \langle \Delta u_{el}^2 \rangle_{\lambda_0}^2 , \quad (7d)$$

where  $\Delta u_{el} = u_{el}(0) - \langle u_{el}(0) \rangle_{\lambda_0}$ . For a Gaussian distribution, all cumulants for  $n \geq 3$  are zero. If the distribution is not Gaussian, the cumulant expansion is infinite or higher-order cumulants diverge, i.e., there does not exist an  $m \geq 3$  such that  $C_m \neq 0$  and  $C_n = 0$  for all  $n > m$ .<sup>13,14</sup> Therefore, the use of only mean and variance in eq 6 would be exact if the underlying distribution were Gaussian. The self-interaction  $u_s$  can be seen to correct the mean and the variance of the  $u_{el}$  distributions. When identical orders of  $\Delta\lambda$  are added in eq 6 we obtain corrected cumulants  $C'_{n, \lambda}$ :

$$C'_{1, \lambda_0} = C_{1, \lambda_0} - 2(\lambda_0 - 1)u_s(0) \quad (8a)$$

$$C'_{2, \lambda_0} = C_{2, \lambda_0} - 2u_s(0)/\beta \quad (8b)$$

$$C'_{m, \lambda_0} = C_{m, \lambda_0} \text{ for } m \geq 3 . \quad (8c)$$

The correction of the variance is independent of the charge state  $\lambda_0$ . The correction of the mean on the other hand is proportional to the charge factor  $1 - \lambda_0$  and vanishes in the uncharged case  $\lambda_0 = 1$ .

We can view eq 6 as a Taylor expansion of the chemical potential around  $\lambda_0$ , where the cumulants contain the information about the derivatives with respect to the coupling parameter  $\lambda$ . We can combine this information about the derivatives in a  $\chi^2$  fit of  $\mu^{ex}(\lambda)$  to a given functional form. We will here use polynomials  $p_l$  of varying order  $l$ . The constant term,  $a_0$ , is undetermined. The coefficients  $\{a_k\}$  will be chosen to minimize a  $\chi^2$  functional,

$$\chi^2(\{a_k\}) = \sum_{n=1}^N \sum_{m=1}^{M_n} [\sigma_n^{(m)}]^{-2} \left[ p_l^{(m)}(\lambda_n, \{a_k\}) - d^{(m)}(\lambda_n) \right]^2, \quad (9)$$

where  $N$  is the number of  $\lambda_n$  values analyzed.  $M_n$  is the number of derivatives calculated at  $\lambda_n$ .  $p_l^{(m)}$  is the  $m$ -th derivative of the polynomial  $p_l(\lambda, \{a_k\}) = \mu^{ex}(\lambda)$  with respect to  $\lambda$ .  $d^{(m)}$  is the observed derivative, which is related to the cumulant  $C'_{m,\lambda}$  through eqs 6 and 8,

$$d^{(m)}(\lambda) = -\beta^{m-1} C'_{m,\lambda}. \quad (10)$$

The estimated statistical error  $\sigma_n^{(m)}$  of  $d^{(m)}(\lambda_n)$  is assumed to be Gaussian.

We can calculate  $u_{el}$  distributions at different charge states  $\lambda$  from simulations of systems with one modified water molecule in a solution of unmodified water. For  $\lambda = 0$ , the statistical efficiency is greatly enhanced since we can average over all water molecules. Using eqs 6, 7, and 9, the cumulant data of the different charge states can be combined to obtain the chemical potential as a function of the coupling parameter  $\lambda$ .

## B. Bennett's overlapping-histogram and acceptance-ratio methods

We also apply Bennett's method of overlapping histograms<sup>1,8,15</sup> to calculate the free energy of uncharging a water molecule. We study two states 0 and 1 with a difference in their configurational energies  $\Delta u = u(\lambda_1) - u(\lambda_0)$ . The normalized probability densities  $p_i(x)$  ( $i = 0, 1$ ) of the energy difference  $\Delta u$  are defined as

$$p_i(x) = \langle \delta(\Delta u - x) \rangle_{\lambda_i}, \quad (11)$$

where  $\delta(x)$  is Dirac's delta distribution.

Canonical-ensemble averages of a function  $A$  of the configuration variables in systems 0 and 1 are related through

$$\langle A \rangle_{\lambda_1} = \frac{\langle A \exp(-\beta \Delta u) \rangle_{\lambda_0}}{\langle \exp(-\beta \Delta u) \rangle_{\lambda_0}}. \quad (12)$$

Using eq 1 we find:

$$\langle A \rangle_{\lambda_1} = \exp(\beta \Delta \mu^{ex}) \langle A \exp(-\beta \Delta u) \rangle_{\lambda_0}. \quad (13)$$

Correspondingly, the probability densities  $p_0$  and  $p_1$  are related through

$$p_1(x) = p_0(x) \exp(\beta \Delta \mu^{ex} - \beta x) \quad (14)$$

with  $\Delta \mu^{ex} = \mu^{ex}(\lambda_1) - \mu^{ex}(\lambda_0)$ . In a region of overlap between  $p_1$  and  $p_0$  one expects a linear dependence of  $\ln[p_1(x)/p_0(x)]$  on  $x$  with slope  $-\beta$  and intercept  $\beta \Delta \mu^{ex}$ .

Applied to the case of uncharging a water molecule, we have

$$\Delta u = -\Delta \lambda u_{el}(0) + \Delta \lambda (\Delta \lambda + 2\lambda_0 - 2) u_s(0). \quad (15)$$

The probability density  $p_0$  can be calculated from histograms of the electrostatic energy  $\Delta u = -u_{el}(0) - u_s(0)$  of water molecules in bulk water (state 0). To calculate  $p_1$ , a system has to be studied comprising one uncharged and  $N - 1$  charged water molecules, where  $u_{el}$  is the fictitious electrostatic energy of the uncharged particle obtained by turning on its charges.  $p_1$  is then the probability distribution of  $\Delta u = -u_{el}(0) - u_s(0)$ .

From eq 13 we find the basic relation of Bennett's acceptance-ratio method to calculate  $\Delta \mu^{ex}$ :<sup>1,8</sup>

$$\beta \Delta \mu^{ex} = \ln \frac{\langle f(-\beta \Delta u + c) \rangle_{\lambda_1}}{\langle f(\beta \Delta u - c) \rangle_{\lambda_0}} + c, \quad (16)$$

where the Fermi function  $f(x) = 1/[1 + \exp(x)]$  has been chosen to minimize the error in the  $\Delta \mu^{ex}$  estimate.  $c$  is an arbitrary constant. Setting it to  $c = \beta \Delta \mu^{ex}$  minimizes the expected error.<sup>8</sup> In a graphical procedure we search for the intersection of the  $\lambda_0$  and  $\lambda_1$  averages in eq 16 as functions of  $c$ . In addition, we expect a plateau for  $\Delta \mu^{ex}$  calculated from eq 16 for  $c$  values close to the optimum  $c = \beta \Delta \mu^{ex}$ . A more detailed discussion of the two methods due to Bennett can be found in refs 1 and 8.

### C. Effective electrostatic interactions

To avoid surface effects, fluid systems are commonly studied using periodic boundary conditions. This results in well-known difficulties regarding the treatment of long-range interactions which are large even at distances comparable to the dimensions of the simulation box. We treat the electrostatic interactions in a truly periodic format by using Ewald lattice summation.<sup>11,16,17</sup> In the Ewald formulation, the electrostatic energy  $U$  of a system comprising  $N$  water molecules carrying partial charges  $q_\alpha$  can be expressed as

$$U = \sum_{1 \leq i < j \leq N} \sum_{\alpha=1}^3 \sum_{\beta=1}^3 q_\alpha q_\beta \varphi_{EW}(\mathbf{r}_{i\alpha j\beta}) + \frac{1}{2} \sum_{i=1}^N \sum_{\alpha=1}^3 \sum_{\beta=1}^3 q_\alpha q_\beta \psi_{EW}(\mathbf{r}_{i\alpha i\beta}) . \quad (17)$$

A lattice vector  $\mathbf{n}$  is added to the distance vector  $\mathbf{r}_{i\alpha j\beta}$  such that  $\mathbf{r}_{i\alpha j\beta} = \mathbf{r}_{j\beta} - \mathbf{r}_{i\alpha} + \mathbf{n}$  is in  $[-L/2, L/2]^3$ .

The self-interaction is defined as  $\psi_{EW}(\mathbf{r}) = \varphi_{EW}(\mathbf{r}) - 1/|\mathbf{r}|$ . The effective Coulomb interaction  $\varphi_{EW}$  can be expressed in terms of rapidly converging lattice sums,

$$\varphi_{EW}(\mathbf{r}) = \sum_{\mathbf{n}} \frac{\text{erfc}(\eta|\mathbf{r} + \mathbf{n}|)}{|\mathbf{r} + \mathbf{n}|} + \sum_{\mathbf{k} \neq 0} \frac{4\pi}{V k^2} \exp\left(-\frac{k^2}{4\eta^2} + i\mathbf{k} \cdot \mathbf{r}\right) - \frac{\pi}{V\eta^2} . \quad (18)$$

$V$  is the volume of the box,  $\text{erfc}$  is the complementary error function, and  $k = |\mathbf{k}|$ . The two lattice sums extend over lattice vectors  $\mathbf{n}$  and  $\mathbf{k}$  of real and Fourier space, respectively.

To calculate the free energy of charging, we need expressions for the electrostatic energy of the system when a single water molecule carries modified charges  $(1-\lambda)q_O$  and  $(1-\lambda)q_H$ . We will identify the difference of the interaction energies  $u(\lambda_1) - u(\lambda_0)$  with the difference of the total energies (eq 17) for the two  $\lambda$  values. Correspondingly, we can write for the interaction energy  $u(\lambda)$  of the modified water molecule  $i = 1$ :

$$u(\lambda) = \sum_{j=2}^N \sum_{\alpha=1}^3 \sum_{\beta=1}^3 (1-\lambda) q_\alpha q_\beta \varphi_{EW}(\mathbf{r}_{1\alpha j\beta}) + \frac{1}{2} (1-\lambda)^2 \sum_{\alpha=1}^3 \sum_{\beta=1}^3 q_\alpha q_\beta \psi_{EW}(\mathbf{r}_{1\alpha 1\beta}) . \quad (19)$$

We identify the first and second sum with  $u_{el}(\lambda)$  and  $u_s(\lambda)$ , respectively. Eq 19 contains self-interactions owing to the presence of lattice images. We can average the self-interactions over the solid angle assuming isotropy. The Ewald potential  $\varphi_{EW}$  can be expanded in spherical harmonics.<sup>10,18,19</sup> In an average of  $\psi_{EW}(\mathbf{r})$  over all orientations, the orthogonality of the spherical harmonics yields only a constant plus an  $r^2$  term,

$$\Psi_{EW}(r) = \int_{\Omega} d\Omega \psi_{EW}(\mathbf{r}) = \xi_{EW} + \frac{2\pi}{3L^3} r^2 , \quad (20)$$

where the constant is  $\xi_{EW} = -2.837297/L$ .<sup>19</sup> From eqs 4 and 19 we obtain for the self-interaction

$$u_s(\lambda) = -(1-\lambda)^2 \frac{2\pi}{3L^3} m^2 \quad (21)$$

where  $m$  is the dipole moment of a water molecule.

In common implementations of Ewald summation, the Fourier-space sum is rewritten such that it scales with the product of the number of particles times the number of  $\mathbf{k}$  vectors.<sup>11</sup> These implementations have the disadvantage that electrostatic potentials at the charge sites are not directly available. To circumvent this problem we use an expansion of the Ewald potential in terms of harmonic functions with cubic symmetry<sup>10,18-20</sup> to calculate the electrostatic potentials  $\phi_O$ ,  $\phi_{H_1}$ , and  $\phi_{H_2}$ . We include in the expansion kubic harmonics up to tenth order. The coefficients are those previously used in the calculation of chemical potentials of restricted-primitive-model ions.<sup>10</sup> They are listed in Table I in the convention of Adams and Dubey.<sup>19</sup> For the calculation of the interaction energies in the Monte Carlo simulations, we do not use the kubic-harmonic approximation but conventional lattice sums.

We also use a generalized reaction-field (GRF) method for the electrostatics.<sup>21,22</sup> The GRF interaction depends only on the distance and has a cutoff length  $r_c$ ,

$$\varphi_{GRF}(r) = \frac{1}{r} p(r/r_c) \Theta(r_c - r) . \quad (22)$$

$\Theta$  is the Heaviside unit-step function;  $p(x)$  is a polynomial:

$$p(x) = (1-x)^4 (1 + 8x/5 + 2x^2/5) . \quad (23)$$

By analogy with Ewald summation (eq 19), we define the  $\lambda$ -dependent energy as

$$u(\lambda) = \sum_{j=2}^N \sum_{\alpha=1}^3 \sum_{\beta=1}^3 (1-\lambda) q_{\alpha} q_{\beta} \varphi_{GRF}(r_{1\alpha j\beta}) + \frac{1}{2} (1-\lambda)^2 \sum_{\alpha=1}^3 \sum_{\beta=1}^3 q_{\alpha} q_{\beta} \Psi_{GRF}(r_{1\alpha 1\beta}) . \quad (24)$$

The self-interaction is defined as  $\Psi_{GRF}(r) = \varphi_{GRF}(r) - 1/r$ . The GRF self-term for an uncharged molecule contains a dominant dipolar contribution  $-4m^2/r_c^3$  and additional terms of higher order in  $r_c^{-1}$ .

The direct electrostatic energy  $u_{el}$  is a sum of pair-additive interactions with the other molecules. It closely resembles the expression from standard electrostatics, with the interaction  $1/r$  being replaced by  $\varphi(\mathbf{r})$ . Based on this resemblance,  $u_{el}$  could form a possible choice in the calculation of energies of charging  $\Delta u$ . The self-term  $u_s$  is a consequence of the difference of the effective interaction  $\varphi(\mathbf{r})$  and  $1/r$ . In the following, we will consistently include the self-term  $u_s$  in the calculation of electrostatic energies. Taking only  $u_{el}$  would be correct for an isolated system, but not when periodic boundary conditions are taken seriously. The direct electrostatic energy  $u_{el}$  stems from the interactions with the other particles in the box (and, in the case of Ewald summation, their periodic images). The self-term  $u_s(\lambda)$  is the difference of the self-interactions with  $\varphi$  as effective potential and the vacuum self-interactions with a  $1/r$  potential (which cancel the infinities of the former). In the case of Ewald summation,  $u_s$  has physical significance as it accounts for the interactions with the images of the water molecule with charges  $(1-\lambda)q_{\alpha}$ . In the context of GRF electrostatics,  $u_s$  is introduced by analogy.

In a previous simulation study, Rick and Berne<sup>9</sup> also used Ewald summation to calculate the free energy of water but with a potential corresponding to vacuum boundary conditions. Their effective potential for  $u_{el}$  calculations differs by  $-2\pi r^2/3V$  (and a constant) from the Ewald potential used here. Correspondingly, the self-interaction of eq 20 then reduces to a constant and the self-term of Rick and Berne for neutral molecules is zero.

### III. COMPUTER SIMULATIONS

We study bulk water ( $\lambda = 0$ ) and a system comprising one uncharged and  $N - 1$  unmodified water molecules ( $\lambda = 1$ ). We use the SPC model of water.<sup>23</sup> Configuration-space averages are performed using the Metropolis Monte Carlo method.<sup>11,24</sup> The systems are studied in the canonical ( $NVT$ ) ensemble. The number density is  $\rho = 33.33 \text{ nm}^{-3}$ . The temperature is kept at  $T = 298 \text{ K}$ . The Monte Carlo move widths is chosen to give an approximate acceptance ratio of 0.5. A cubic box under periodic boundary conditions is used for the simulations. The system size is varied between  $N = 256, 64$ , and 32 water molecules to study finite-size effects.

The long-range electrostatic interactions are treated using Ewald summation.<sup>11,16,17</sup> The real-space screening factor is set to  $\eta = 5.6/L$  ( $L$  is the length of the box). The real-space interactions are truncated at  $L/2$ . The Fourier-space sum is spherically truncated using  $\mathbf{k}$  vectors with  $|\mathbf{k}|^2 \leq 38(2\pi/L)^2$ , resulting in  $2 \times 510$   $\mathbf{k}$  vectors considered.<sup>25</sup> The background dielectric constant is corrected from infinity to  $\epsilon_{RF} = 65$  by adding a term  $2\pi \mathbf{M}^2 / (2\epsilon_{RF} + 1)V$  to the potential energy, where  $\mathbf{M}$  is the total dipole moment of the simulation box.

We also perform simulations using the GRF interaction. A cutoff of  $r_c = 0.9 \text{ nm}$  ( $N = 256$ ) and  $r_c = L/2$  ( $N = 64$ ) is used. Again, a correction term for a finite dielectric background is added to the total energy. In all simulations, periodic boundary conditions are applied with respect to atomic sites. As starting structures we use randomly oriented and positioned water molecules or final structures or previous runs. Before averaging, the systems are extensively equilibrated.

To calculate the electrostatic energy of charging an uncharged water molecule, systems are studied comprising  $N - 1$  SPC water molecules and one uncharged Lennard-Jones sphere with water parameters. The number density is  $\rho = 33.33 \text{ nm}^{-3}$ . At regular intervals, the electrostatic energy is calculated for 50 random orientations of a fictitious charged molecule with the oxygen position identical to the uncharged Lennard-Jones particle.

### IV. RESULTS AND DISCUSSION

We will first present results for the statistical distribution of  $u_{el}$ . Figure 1 shows histograms of  $u_{el}$  for the charged and uncharged state calculated using  $N = 256$  particles and Ewald summation. The histograms are shown on a logarithmic scale so that Gaussians appear as parabolas. Also shown are Gaussian distributions with identical mean and variance. The distribution in the charged case ( $\lambda = 0$ ) is approximately Gaussian, but more centered. It decays faster than Gaussian and has a negative kurtosis. The distribution in the uncharged case ( $\lambda = 1$ ) on the other hand deviates more strongly from a Gaussian form. It is skewed, has weakly decaying tails and, correspondingly, a positive kurtosis.

Table II lists the cumulants  $C_{n,\lambda}$  of  $u_{el}$  for simulations with  $\lambda = 0$  and 1. Results are shown for Ewald-summation and GRF electrostatics and for system sizes of  $N = 32, 64$ , and 256 molecules. The results for small system sizes are included to study the dependence of the cumulants on electrostatic interaction and system-size, as we are ultimately interested in the thermodynamic limit. The consideration of the self-term greatly reduces the variation for the averages  $C_{1,\lambda=0}$ . The uncorrected Ewald-summation results for  $N = 32, 64$ , and 256 range between  $-96.69$  and  $-98.00 \text{ kJ mol}^{-1}$ . With the self-term added, the range is  $-98.05$  to  $-98.17 \text{ kJ mol}^{-1}$ , compared to a typical statistical error of  $0.1 \text{ kJ mol}^{-1}$ .<sup>26</sup> The GRF self-term is significantly

larger than that of Ewald summation. The corrected value  $C'_{1,\lambda=0}$  of the GRF simulation with  $N = 256$  agrees with the Ewald-summation result within the statistical errors. The corrected  $N = 64$  result for  $C'_{1,\lambda=0}$  is somewhat too negative, but in much better agreement with the Ewald-summation data (1 versus 10 kJ mol<sup>-1</sup> difference).

On the other hand, the variance data  $C_{2,\lambda}$  from Ewald-summation simulations do not show a clear improvement by addition of the self-term. However, this is not conclusive since the corrections are of the size of the statistical error or smaller. The improvement by addition of the self-term is more evident in the GRF variances. The higher cumulants  $C_{3,\lambda=0}$  and  $C_{4,\lambda=0}$  show less system-size dependence. Results for different system sizes and electrostatics agree within statistical errors. A possible exception is that the GRF values for  $C_{3,\lambda=0}$  are too small. Overall, the first four cumulants of the charged state ( $\lambda = 0$ ) can be calculated accurately for systems with as few as  $N = 64$  (and possibly  $N = 32$ ) water molecules using Ewald summation if the finite-size corrections are applied.

We use the cumulants  $C'_{1,\lambda}$ ,  $C'_{2,\lambda}$ ,  $C_{3,\lambda}$ , and  $C_{4,\lambda}$  for the charged ( $\lambda = 0$ ) and uncharged ( $\lambda = 1$ ) case of the  $N = 256$  simulations to calculate the chemical-potential difference  $\Delta\mu^{ex}$  of uncharged and charged water. The cumulants  $C_{4,\lambda}$  for  $\lambda = 0$  and 1 (see Table II) differ significantly. Therefore, we have to use fitting polynomials of order five or higher in the  $\chi^2$  fit eq 9. Results for  $\Delta\mu^{ex}$  are listed in Table III. The polynomial  $p_8$  of order 8 is interpolating, i.e.,  $p_8$  fits the data exactly. The results for polynomials  $p_5$  to  $p_8$  vary between  $\Delta\mu^{ex} = 35.13$  and  $35.80$  kJ mol<sup>-1</sup>, or by about 2 %. The Ewald and GRF results for like orders differ by less than  $0.09$  kJ mol<sup>-1</sup> (0.25 %). The interpolating polynomials  $p_8$  yield  $35.60$  (Ewald) and  $35.63$  kJ mol<sup>-1</sup> (GRF) for  $\Delta\mu^{ex}$ . From block averages, we estimate the statistical errors of the  $p_8$  data for  $\Delta\mu^{ex}$  to be  $0.15$  kJ mol<sup>-1</sup>.

We will now compare the results from polynomial fits with those obtained from Bennett's method of overlapping histograms.<sup>8</sup> Figure 2 shows the ratio  $\ln(p_1/p_0)$  of the probabilities as a function of  $\Delta u = u(\lambda_1) - u(\lambda_0)$ , as described above. The distributions  $p_1$  and  $p_0$  are calculated from histograms of  $u_{el}$  using a bin widths of  $0.1$  kJ mol<sup>-1</sup>. Self-interactions are added and the sign is inverted according to eq 15. In the overlap region of the distributions, we indeed find the expected linear behavior  $\ln(p_1/p_0) = \beta(\Delta\mu^{ex} - \Delta u)$ . We fit constants  $\Delta\mu^{ex} = 35.63$  and  $35.60$  kJ mol<sup>-1</sup> to the Ewald-summation and GRF data for  $20 \leq \Delta u \leq 50$  kJ mol<sup>-1</sup>, respectively. The  $\Delta\mu^{ex}$  values are in excellent agreement with  $\Delta\mu^{ex} = 35.60$  (Ewald) and  $35.63$  kJ mol<sup>-1</sup> (GRF) calculated from the polynomials  $p_8$  interpolating the derivative data.

Also included in Figure 2 are the results of Gaussian approximations to the probability densities. However, as expected from the significant deviations from Gaussian behavior found in Figure 1, we do not observe a linear regime. This provides evidence for the failure of a simple Gaussian picture of the fluctuation statistics for the hydration of water. Assumption of Gaussian behavior (or, correspondingly, quadratic dependence on the coupling parameter) results in inaccurate estimates of the chemical-potential difference  $\Delta\mu^{ex}$ .

Bennett's acceptance-ratio method<sup>8</sup> yields  $35.59$  (Ewald) and  $35.60$  kJ mol<sup>-1</sup> (GRF) for  $\Delta\mu^{ex}$ . These values are calculated by searching for the intersection of the Fermi-function averages for  $\lambda = 0$  and 1 in eq 16. The corresponding value of  $c$  is identified with the difference in the chemical potential,  $\beta\Delta\mu^{ex} = c$ . The averages are calculated from the tabulated histogram data for  $\Delta u$ . The acceptance-ratio values of  $\Delta\mu^{ex}$  are again in excellent agreement with those calculated using the interpolating polynomial  $p_8$ .

Rick and Berne<sup>9</sup> calculated  $\Delta\mu^{ex}$  by evaluating  $C_{1,\lambda}$  at different charge states  $-0.22 \leq \lambda \leq 1$  and combining the data by numerical integration. This is essentially a variant of the method we are using in this work. However, inclusion of accurately sampled cumulants of higher order—as is done here—should decrease the number of  $\lambda$  points required. From eleven molecular dynamics simulations of 40 ps duration with  $N = 512$  SPC water molecules, Rick and Berne find  $\Delta\mu^{ex} = 35.15 \pm 2.1$  kJ mol<sup>-1</sup>, in agreement with our data.

Figure 3 shows the chemical potential  $\Delta\mu^{ex}$  as a function of the charge coupling parameter  $\lambda$ . Results are shown for the interpolating polynomials  $p_8$  of the Ewald-summation and GRF data, which are practically indistinguishable. Also shown are the data of Rick and Berne,<sup>9</sup> which are found to agree with the  $p_8$  curves. We find agreement also in the region  $\lambda < 0$ , where the polynomials  $p_8$  are extrapolating the data at  $\lambda = 0$  and 1.

The parabolic  $\Delta\mu^{ex}$  curves obtained by assuming Gaussian-fluctuation statistics are included in Figure 3. The quadratic expansions around both the charged and uncharged state are accurate only for small perturbations  $|\Delta\lambda| < 0.3 - 0.4$ . For larger perturbations, the parabolas show large deviations from the fitted polynomials and the data of Rick and Berne. This provides further evidence for the failure in the large-perturbation regime of simple models, which represent the chemical potential as quadratic functions of the coupling parameter based on the assumption of Gaussian-fluctuation statistics.

Also shown in Figure 3 are the results of direct calculations using eq 1, which can be rewritten for the case of uncharging water as

$$\mu^{ex}(\lambda_1) - \mu^{ex}(\lambda_0) = -k_B T \ln \langle \exp[\beta(\lambda_1 - \lambda_0)u_{el}(0)] \rangle_{\lambda_0} + \Delta\lambda(\Delta\lambda + 2\lambda_0 - 2)u_s(0). \quad (25)$$

Correspondingly, the direct calculation determines the logarithm of the characteristic function of the distribution of electrostatic energies  $u_{el}(0)$ . We can see that the exponential average for both  $\lambda_0 = 0$  and 1 works well for small perturbations  $|\lambda_1 - \lambda_0| < 0.5$ . For larger perturbations, the direct method fails. Expansions around the charged and uncharged state predict values for the difference in chemical potential which are too large by about 2.8 and too small by about 6.8 kJ mol<sup>-1</sup>, respectively.

However, by fitting polynomials to the derivatives at the two ends  $\lambda = 0$  and 1 of the interval, we essentially attempt to connect the two curves smoothly near  $\lambda = 0.5$ . This explains the success of the method based on fluctuation statistics: We can accurately combine information of two widely separated states by smoothly connecting the curves from direct averages near  $\lambda = 0.5$ , where they are still accurate. Using higher-order cumulants which can be sampled accurately in this case since they

are significantly different from zero allows us to construct a non-trivial form of the chemical potential as a function of charge. This charging function deviates strongly from a simple quadratic form, in agreement with previous observations by Rick and Berne<sup>9</sup> and with large values of the kurtosis  $C_4/C_2^2$  of the  $u_{el}$  distributions.

The idea of smoothly connecting the curves from direct calculations can be turned into an algorithm. We shift the  $\lambda = 1$  curve  $\gamma_1(\lambda) = -k_B T \ln \langle \exp[-\beta u(\lambda) + \beta u(1)] \rangle_1$  vertically by  $\Delta\mu^{ex}$  and determine the intersection with the  $\lambda = 0$  curve  $\gamma_0(\lambda) = -k_B T \ln \langle \exp[-\beta u(\lambda) + \beta u(0)] \rangle_0$ . We then calculate the first derivatives of the two curves at the intersection from polynomial interpolation. The absolute value of the difference  $\Delta = \gamma'_1(\bar{\lambda}) - \gamma'_0(\bar{\lambda})$  between the two derivatives is minimized with respect to the vertical shift,

$$\min_{\Delta\mu^{ex}} |\gamma'_1(\bar{\lambda}) - \gamma'_0(\bar{\lambda})|, \quad (26)$$

where  $\bar{\lambda}$  is the solution of  $\gamma_0(\bar{\lambda}) = \gamma_1(\bar{\lambda}) + \Delta\mu^{ex}$ .  $|\Delta|$  is plotted in Figure 4 as a function of the chemical-potential difference  $\Delta\mu^{ex}$  between the charged and uncharged state. The difference in the derivatives shows a distinct minimum for  $\Delta\mu^{ex}$  between 35.7 and 35.8 kJ mol<sup>-1</sup>. This result is in excellent agreement with the previously calculated numbers, deviating by less than 0.1 %. This simple, geometrical analysis can therefore complement the more elaborate methods and provide accurate results for the chemical potential.

We can also use this analysis to choose an optimal  $\lambda$  value in the interval  $[\lambda_0, \lambda_1]$  to improve the accuracy of the results. From the  $|\Delta|$  dependence on the  $\bar{\lambda}$ -value of intersection of the two curves  $\gamma_0(\bar{\lambda})$  and  $\gamma_1(\bar{\lambda}) + \Delta\mu^{ex}$ , we find that the smoothest connection occurs for  $\bar{\lambda} \approx 0.45 - 0.5$ . For the purpose of calculating free energies, it would be interesting to perform a single simulation at  $\lambda = 0.5$  (i.e., for a water molecule carrying 0.5 times the full charges). Judging from the previous results, a simulation at  $\lambda = 0.5$  should produce sufficient information to calculate the chemical potential on the whole interval  $0 \leq \lambda \leq 1$ . However, in this work we restrict our analysis to the physically more relevant systems of bulk water ( $\lambda = 0$ ) and an uncharged solute in water ( $\lambda = 1$ ).

Another observation of this study is the importance of the inclusion of self-terms as approximate corrections for finite-size effects. Included in Table III are the  $\Delta\mu^{ex}$  values calculated from polynomial fits to the data of the  $N = 64$  simulations using Ewald summation. The values of the  $N = 64$  and  $N = 256$  systems agree closely. The difference of the  $p_8$  data is 0.04 kJ mol<sup>-1</sup> compared to estimated statistical errors of 0.15 kJ mol<sup>-1</sup>. On the other hand, the  $p_8$  values for the uncorrected cumulant data (i.e., without self-terms) are 35.22 ( $N = 64$ ) and 35.52 kJ mol<sup>-1</sup> ( $N = 256$ ), differing by 0.3 kJ mol<sup>-1</sup>. Addition of the self-term results in a reduced system-size dependence.

The improvement is even more evident when we compare results from simulations using different electrostatic interactions. The difference in chemical potential  $\Delta\mu^{ex}$  of charged and uncharged state calculated from the polynomial fit  $p_8$  and Bennett's overlapping-histogram and acceptance-ratio methods agree within 0.04 kJ mol<sup>-1</sup> for GRF and Ewald-summation data if self-terms are added. Without the self-terms they would differ by about 1.7 kJ mol<sup>-1</sup>. In addition, also the chemical potential as a function of the charge shown in Figure 3 is identical in the range of  $\lambda$  considered. This shows that even with less sophisticated methods for the electrostatics such as GRF compared to Ewald summation it is possible to calculate charge-related free energies accurately if only self-terms are considered consistently.

## V. CONCLUSIONS

Using fluctuation statistics of two equilibrium simulations (bulk water and water hydrating an uncharged Lennard-Jones particle) we are able to calculate accurately the chemical potential of SPC water as a function of its charge. Bennett's overlapping-histogram and acceptance-ratio methods<sup>8</sup> and a geometrical method based on smoothly connecting the curves of direct, exponential averages at the two states give identical results for the chemical-potential difference between charged and uncharged water. Our results agree with those of Rick and Berne<sup>9</sup> calculated from thermodynamic integration using eleven states with respect to both the chemical-potential difference and the dependence on the charge.

We find significant deviations from a quadratic dependence of the chemical potential on the charge coupling parameter. This has important implications. It shows that even for the fairly simple system of water in water second-order perturbation or, equivalently, assumption of Gaussian-fluctuation statistics, allow only crude descriptions of the actual thermodynamics. This also affects the potential usefulness of linear continuum models of electrostatics,<sup>2,9,27-30</sup> which by design do not go beyond a quadratic behavior. However, when calculating free-energy differences, continuum models usually compare approximate representations of physical states rather than performing an *expansion* around a single state. This can explain their success of giving at least approximately correct free-energy values even in the presence of strongly non-linear dependencies in a corresponding system of atomic resolution.<sup>9</sup>

In addition to the failure of the simple Gaussian model, expansions around only a single state using higher-order cumulants are expected to fail.<sup>31</sup> Increasing the order of the perturbation requires accurate information about the poorly sampled tails of distributions. This merely reflects the difficulty to *extrapolate* to states that strongly differ in their structure and fluctuation statistics. *Interpolation* on the other hand is in general a much simpler task and allows more accurate predictions. In this work we effectively combine the information of two states to derive a polynomial expression for the chemical potential.

An important point concerns the treatment of electrostatic interactions in computer simulations of systems under periodic boundary conditions. With respect to system-size dependence and electrostatic model, we obtain consistent results using Ewald summation and a generalized reaction-field model. But consistency is only achieved if self-interactions are included. These self-interactions arise naturally when effective potentials are used for the Coulomb interactions. We made similar observations in previous studies of the chemical potential of ions.<sup>3,10</sup> Adding self-terms to the energies acts as an effective correction for effects of a finite system size. Neglecting them can result in significant deviations for small systems of a few hundred particles.

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FIG. 1. Probability density of the electrostatic energy  $u_{el}$  of a water molecule with full charge ( $\lambda = 0$ ; centered near  $u_{el} = -100 \text{ kJ mol}^{-1}$ ) and with zero charge, where fictitious charges are turned on ( $\lambda = 1$ ; centered near  $u_{el} = 0$ ). The probabilities are shown on a logarithmic scale such that Gaussians appear as parabolas. Also shown are Gaussian distributions (dot-dashed lines) with mean and variance equal to the calculated distributions. The distributions are calculated from Monte Carlo simulations using  $N = 256$  particles with Ewald summation. The curves do not contain corrections for self-interactions.

FIG. 2. Bennett’s method of overlapping histograms.<sup>8</sup> The ratio  $\ln(p_1/p_0)$  of the probabilities is shown with crosses as a function of  $\Delta u = u(\lambda_1 = 1) - u(\lambda_0 = 0)$ .  $p_1$  and  $p_0$  are approximated by histogram values calculated from Ewald-summation and GRF simulations using  $N = 256$  particles. The GRF data are shifted vertically by  $-10$ . Also shown are lines with slope  $-\beta$  fitting the data. The dot-dashed lines represent the results of a Gaussian approximation (see Figure 1) with mean and variance taken from the GRF and Ewald-summation data.

FIG. 3. The chemical potential  $\Delta\mu^{ex}$  of water as a function of its charge.  $\lambda = 0$  and  $1$  correspond to the fully charged and uncharged state, respectively. Solid lines are polynomials of order 8 fitted to the cumulants  $C'_{1,\lambda}$ ,  $C'_{2,\lambda}$ ,  $C_{3,\lambda}$ , and  $C_{4,\lambda}$  for  $\lambda = 0$  and  $1$ . The curves for Ewald-summation and GRF data are practically indistinguishable. Shown as symbols with error bars are the data of Rick and Berne taken from Figure 2 of ref 9. Also shown are results from direct calculations using eq 25. The expansion around charged and uncharged state  $\lambda = 0$  and  $\lambda = 1$  are shown with dashed and dot-dashed lines, respectively, in both cases using the data of Ewald-summation simulations. The dotted lines represent quadratic expansions around  $\lambda = 0$  and  $1$  using mean and variance of the Ewald-summation data and assuming Gaussian statistics.

FIG. 4. Smooth connection of the chemical-potential curves. Two curves for the chemical potential are calculated from direct, exponential averages eq 25 for the charged and uncharged state. One of the curves is shifted vertically and the intersection of the two curves is calculated. Shown is the absolute value of the difference  $\Delta$  of the first derivatives at the intersection as a function of the corresponding difference in chemical potential  $\Delta\mu^{ex}$ . Where  $|\Delta|$  reaches a minimum, the two curves can be connected most smoothly. This determines an estimated value for the chemical-potential difference between charged and uncharged water  $\Delta\mu^{ex} = 35.7 - 35.8 \text{ kJ mol}^{-1}$ .

TABLE I. Expansion-coefficients  $S$  and  $A_l$  of the Ewald potential  $\varphi_{EW}(\mathbf{r})$  in terms of kubic-harmonic functions<sup>10</sup> in the convention of Adams and Dubey.<sup>19</sup> The constant  $S$  has been adjusted from its exact value such that the numerical scheme gives a vanishing average potential of a point charge in a cube.

$S$	$-2.8373002368$
$A_2$	$2\pi/3$
$A_4$	$7.718196$
$A_6$	$20.657378665$
$A_8$	$86.85346475$
$A_{10}$	$179.631024892$

TABLE II. Cumulants of the  $u_{el}$  distributions calculated from Monte Carlo simulations using  $N$  particles. The cumulants were averaged over  $P$  passes, where one pass consists of  $N$  attempted moves (i.e., one attempted Monte Carlo move per particle). Coulomb denotes the treatment of electrostatic interactions. The fully charged and uncharged water molecules correspond to  $\lambda = 0$  and  $\lambda = 1$ .  $C_k$  denotes the  $k$ -th cumulant of the distribution [measured in  $(\text{kJ mol}^{-1})^k$ ]. The cumulants with corrections for the self-interaction are listed as  $C'_k$ .

$N$	Coulomb	$P/1000$	$\lambda$	$C_1$	$C'_1$	$C_2$	$C'_2$	$C_3$	$C_4$
256	EW	280	0	$-98.00(10)$	$-98.17(10)$	$439.5(2.0)$	$440.0(2.0)$	$120(50)$	$-25400(1000)$
64	EW	860	0	$-97.47(10)$	$-98.15(10)$	$439.7(2.0)$	$441.4(2.0)$	$102(60)$	$-24900(1500)$
32	EW	860	0	$-96.69(15)$	$-98.05(15)$	$443.4(3.0)$	$446.8(3.0)$	$100(90)$	$-27200(2500)$
256	GRF	460	0	$-94.73(10)$	$-98.22(10)$	$434.5(1.5)$	$443.1(1.5)$	$62(50)$	$-24400(1000)$
64	GRF	900	0	$-88.36(10)$	$-99.05(10)$	$418.3(1.5)$	$444.7(1.5)$	$21(40)$	$-23650(1000)$
256	EW	280	1	$-0.006(5)$	$-0.006(5)$	$110.0(2.0)$	$110.4(2.0)$	$261(20)$	$13000(1000)$
64	EW	1000	1	$-0.007(5)$	$-0.007(5)$	$109.5(3.0)$	$111.2(3.0)$	$263(15)$	$12500(1000)$
256	GRF	600	1	$0.16(2)$	$0.16(2)$	$106.4(2.0)$	$115.1(2.0)$	$277(20)$	$12450(1000)$

TABLE III. Difference in chemical potential  $\Delta\mu^{ex}$  of an uncharged and charged water molecule in water. Results from  $\chi^2$  fits of polynomials  $p_n$  of order  $n$  to the derivative data of the  $N = 256$  simulations using Ewald-summation (EW-256) and GRF interactions. Also included are results for the  $N = 64$  simulations using Ewald summation (EW-64).  $\Delta\mu^{ex}$  is listed in kJ mol $^{-1}$ . The statistical errors of the  $p_8$  data are estimated to be 0.15 kJ mol.

	EW-256	EW-64	GRF
$p_5$	35.46	35.23	35.45
$p_6$	35.13	35.05	35.22
$p_7$	35.76	35.71	35.80
$p_8$	35.60	35.56	35.63

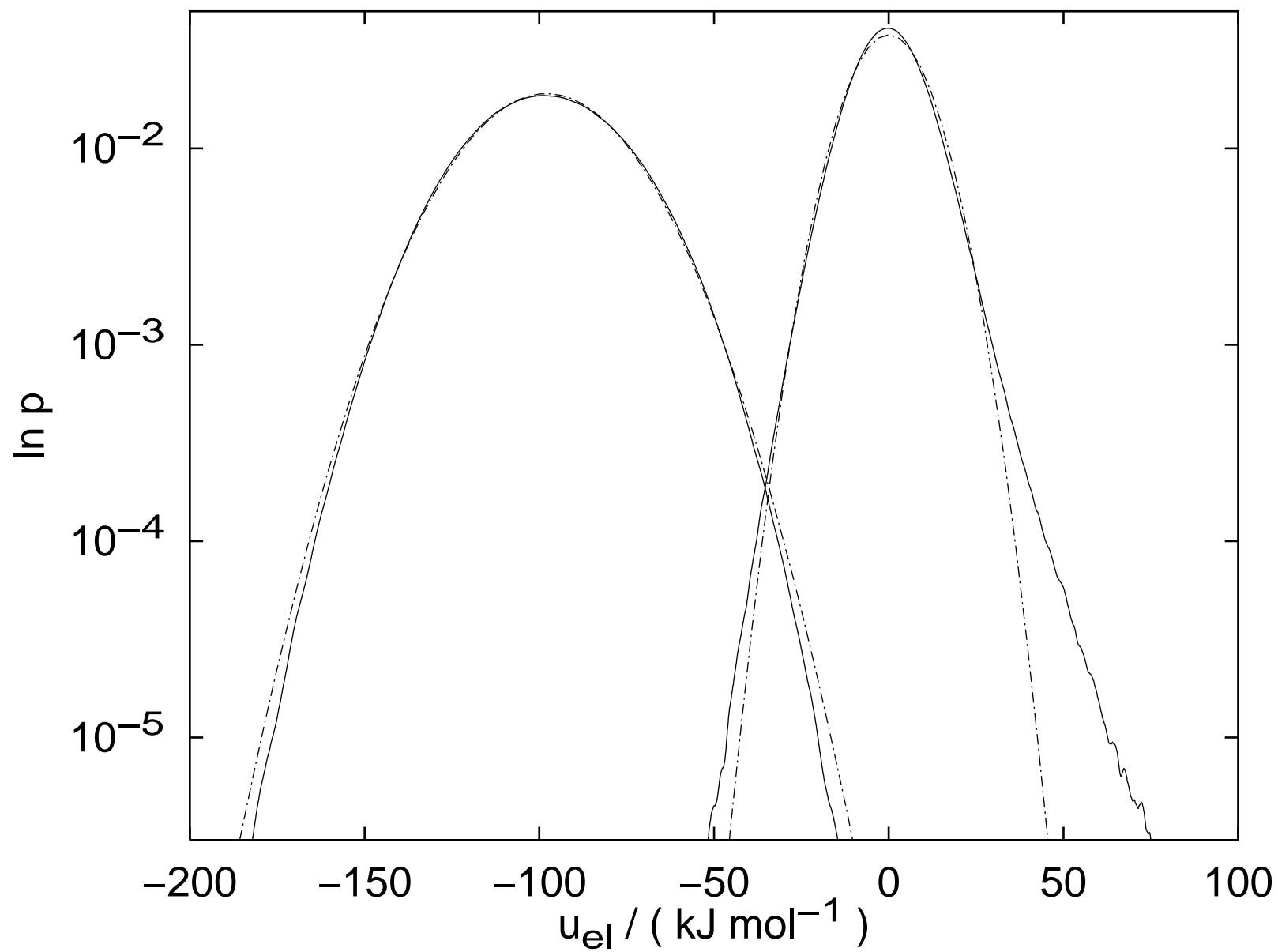


Fig. 1 (Hummer, Pratt, and Garcia)

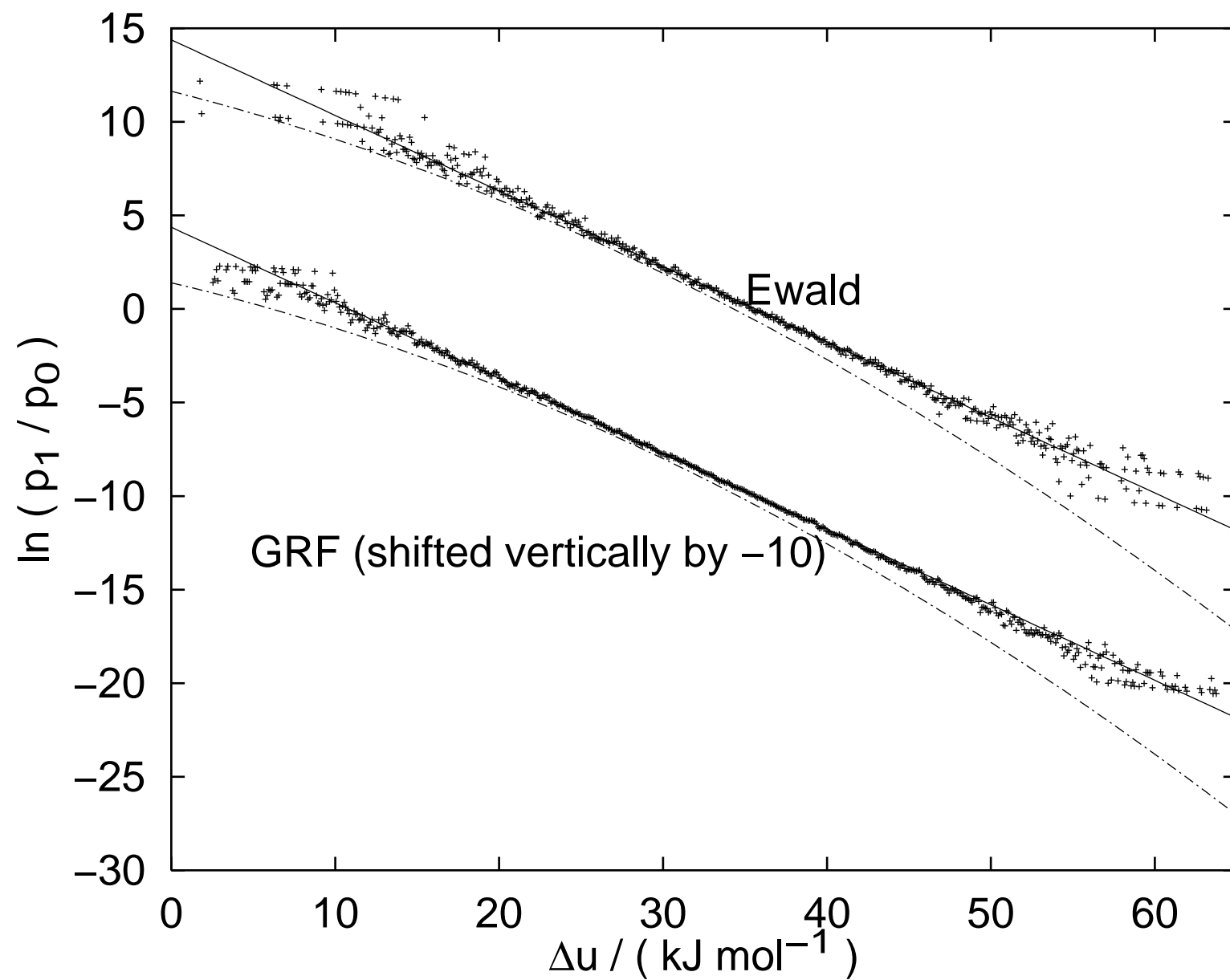


Fig. 2 (Hummer, Pratt, and Garcia)

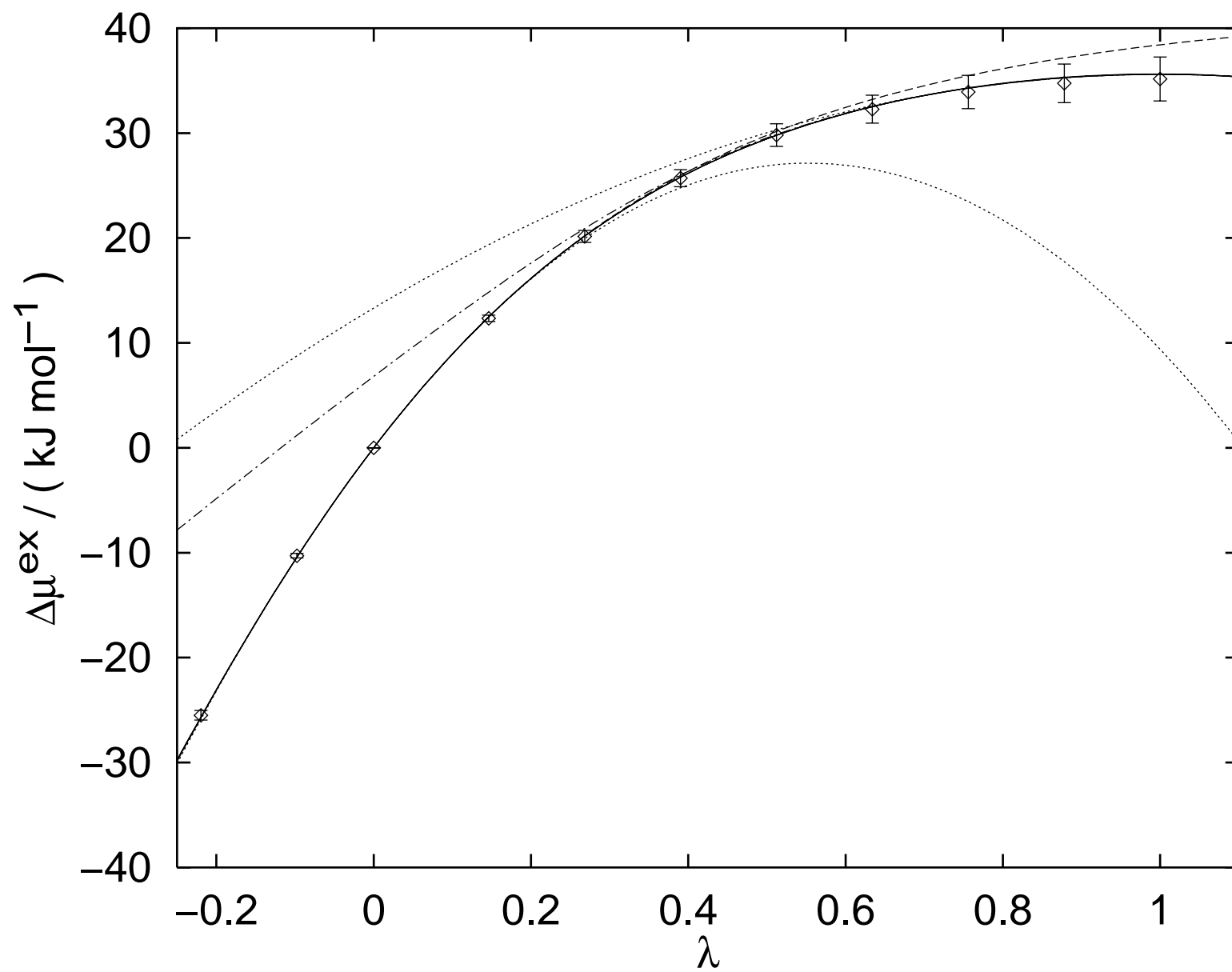


Fig. 3 (Hummer, Pratt, and Garcia)

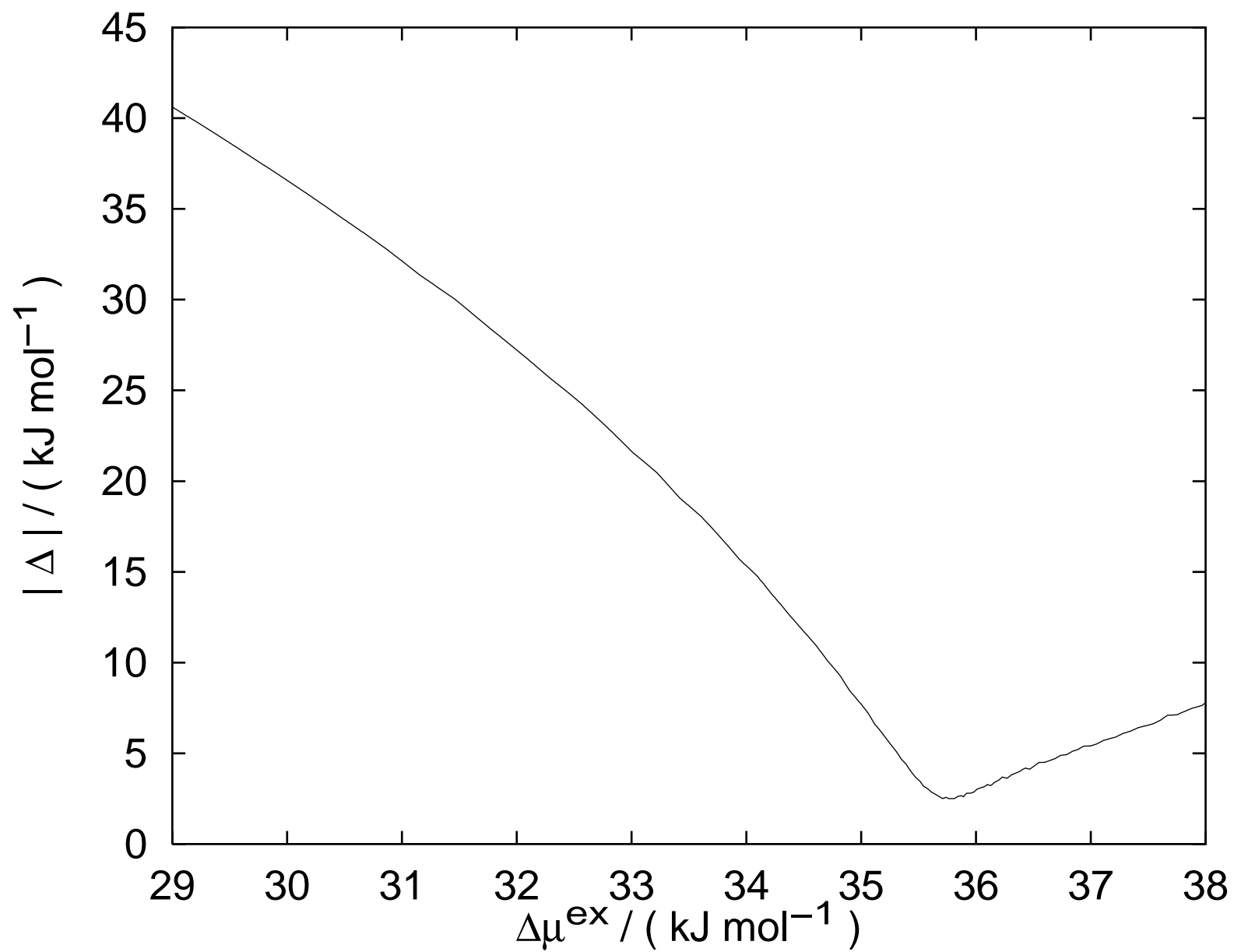


Fig. 4 (Hummer, Pratt, and Garcia)